REMARKS

Status of the Claims

Claims 1, 3, 4, 6-8, 10, 27, 29, and 30 were pending in the present application. Applicants have amended claims 3 and 4. Upon entry of this amendment, claims 1, 3, 4, 6-8, 10, 27, 29, and 30 will be pending and are presented for consideration.

Claim Amendments

Applicants have amended claim 3 to correct a typographical error. Applicants have amended claim 4 to recite that the portion of the IgG3 constant region comprises a mutation or deletion. Support for claim 4 as amended can be found throughout the specification, at least, for example, at page 3, lines 20-22. Applicants submit that these amendments introduce no new subject matter.

Claim Rejections Under 35 U.S.C. § 101

Claims 1, 3, 6-8, 10, 29, and 30 were rejected under 35 U.S.C. § 101 as allegedly claiming non-statutory subject matter. Applicants respectfully traverse the rejection as applied to the rejected claims and submit that a "region" of a gene construct is statutory subject matter under 35 U.S.C. § 101.

The scope of 35 U.S.C. § 101 has been interpreted by the U.S. Supreme Court to be expansive so as to include "anything under the sun that is made by man." Diamond v. Chakrabarty, 447 U.S. 303, 308-309 (1980). The Supreme Court further stated that "[i]n choosing such expansive terms as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplated that the patent law would be given wide scope." Chakrabarty, 447 U.S. at 308-309. While this scope must still fall within the meaning of 35 U.S.C. § 101, "it is improper to read into section 101 limitations as to the subject matter that may be patented where the legislative history does not indicate Congress clearly intended such limitations." In re Alappat, 33 F.3d 1526, 1542 (Fed. Cir. 1994). The only limitations on subject matter determined by the courts to be outside the scope of § 101 are abstract ideas, laws of nature and natural phenomena. MPEP § 2106. Applicants submit that "a region of a gene construct"

does not fall into any of these judicially excluded categories, but rather falls under the purview of the statutory categorizations of composition of matter or manufacture.

Firstly, applicants submit that the claimed "region of a gene construct" is a composition of matter as defined in *Chakrabarty,* namely "a composition of two or more substances [or]...a[] composite article, whether [it] be the result[] of chemical union, or of mechanical mixture, or whether...[it] be [a] gas [], fluid[], powder[], or solid[]." Chakrabarty, 447 U.S. at 308. The region of a gene construct as claimed is a composite article that is the result of a man-made chemical union of a segment of DNA encoding an immunoglobulin polypeptide and a segment of DNA encoding a non-immunoglobulin polypeptide. In fact, the declaration of Drs. Lo and Gillies, filed January 14, 2004, demonstrates how the claimed region was constructed, thus creating the composite article. Applicants therefore submit that the claimed region of a gene construct falls within the statutory scope of 35 U.S.C. § 101.

Furthermore, Applicants submit that the region of a gene construct as claimed is also a manufacture within the purview of 35 U.S.C. § 101. As defined in *Chakrabarty*, a manufacture is "the production of articles for use from raw or prepared materials by giving to these materials new forms, qualities, properties or combination, whether by hand labor or machinery." Chakrabarty, 447 U.S. at 308. Applicants submit that the evidence in the declaration of Drs. Lo and Gillies demonstrates how the DNA forming the claimed region of a gene construct was crafted to create a new combination of DNA encoding a peptide with an immunoglobulin and an IL-2 moiety. Therefore, Applicants submit that the claimed region of a gene construct is an article of manufacture within the scope of 35 U.S.C. § 101. In light of these arguments, Applicants request reconsideration and withdrawal of the rejection of claims 1, 3, 6-8, 10, 29, and 30 under 35 U.S.C. § 101.

Claim Rejection Under 35 U.S.C. § 112, 2nd Paragraph

Claim 4 was rejected under 35 U.S.C. § 112, 2nd paragraph. Applicants respectfully traverse the rejection. Applicants have amended claim 4 as the Examiner suggested. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Claim Rejections Under 35 U.S.C. § 103(a)

Gray and Harvill

Claims 1, 3, 6-8, 10, 27, 29, and 30 were rejected as allegedly unpatentable under 35 U.S.C. § 103(a) over Gray *et al.* (U.S. Patent No. 6,444,792) ("Gray") in view of Harvill *et al.* (1995), Immunotechnology, 1(2): 95-105 ("Harvill"). Applicants respectfully traverse the rejection as applied to the pending claims.

Claim 1 and those claims depending therefrom (3, 6-8, 10, 29, and 30) are directed to a region of a gene construct encoding an antibody-based fusion protein including, at its 5' end, nucleotides encoding at least a portion of an IgG1 or IgG3 CH2 domain, with a mutation or a deletion reducing binding affinity for an Fc receptor, and at the 3' end, nucleotides encoding a non-Ig protein. As acknowledged by the Examiner, Gray does not teach an immunoglobulin fusion protein in that orientation. However, the Examiner suggests there is a motivation to combine Gray with Harvill to produce the Applicants' claimed invention because Gray teaches antibody-based fusion proteins having an increased serum half-life and Harvill teaches that the therapeutic value of IL-2 is limited by its short half-life.

Applicants submit that the deficiencies of Gray cannot be remedied by the addition of Harvill because there is no motivation to modify Gray to incorporate the IL-2 of Harvill in the Ig-IL-2 orientation taught by Harvill. The CTLA4-Ig fusion proteins of Gray are designed to decrease stimulation of the immune system. Gray teaches that the CTLA4-Ig fusion proteins of the invention inhibit T cell activation by inhibiting the interaction of CTLA4 ligands with T cell receptors. (See Gray, *e.g.* col. 3, lines 27-32; col. 5, lines 18-24; col. 18, lines 8-16). Gray also teaches that immunoglobulin constant region-mediated effector functions are undesirable and, if modified, would likely result in a CTLA4-Ig fusion protein with improved immunoinhibitory properties. (See Gray, col. 3, lines 35-45). On the other hand, Harvill teaches an IgG3-IL-2

fusion protein. IL-2 is known in the art to induce T cell proliferation, and thus performs an immunostimulatory function. Further, Harvill teaches that the "therapeutic value of IL-2 lies in its ability to stimulate an immune response, including generating increased cytotoxic activity from a variety of immune cells" (Harvill, pg. 103, col. 2). Therefore, Harvill provides no motivation to modify Gray's fusion protein to incorporate IL-2 at the 3' end because such a modification would interfere with the intended immunoinhibitory properties of Gray's fusion protein. "If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP § 2143.01. Applicants therefore submit that even in combination, Gray and Harvill cannot render the claimed invention obvious.

Furthermore, Applicants submit that the deficiencies of Harvill cannot be remedied by the addition of Gray. Harvill teaches an IgG3-IL2 fusion protein, but does not teach a mutation or deletion reducing Fc receptor binding. Gray teaches mutating the constant region to reduce Fc receptor binding. Applicants submit that there is no motivation to modify Harvill to reduce Fc receptor binding because the modification would render it unsatisfactory for its intended purpose. The IgG3-IL-2 fusion protein of Harvill is "designed to combine the antigen specificity and effector functions of human IgG3 with the immune stimulatory activities of IL-2" (Harvill, pg. 102, col. 2, emphasis added). Harvill was motivated to design the molecule to retain effector functions because "the simultaneous triggering of cell mediated immunity through IL-2 and Fc-mediated effector functions through the antibody could further improve immune stimulation" (Harvill, pg. 96, col. 2). Harvill shows that the fusion protein maintained and in some cases improved immune stimulation, as intended:

> The work presented here shows that IgG3-IL2 activates complement, binds...FcγRI and IL-2R and stimulates both proliferation and cytotoxicity. The noted increases in LAK generation and binding to the high affinity IL-2R($\alpha\beta\gamma$) are unexpected findings that highlight the importance of the careful characterization of these molecules. (Harvill, pg.104, col. 2)

Gray, in contrast, teaches that "immunoglobulin constant region-mediated biological effector mechanisms, such as a complement mediated cell lysis, Fc receptor-mediated phagocytosis or antibody-dependent cellular cytoxicity, may induce detrimental side effects...and

are therefore undesirable." (Gray, col. 3, lines 36-40, emphasis added). Because mutating the Fc region of Harvill's fusion protein to reduce Fc mediated effector functions would render the protein unsatisfactory for its intended purpose (performing effector functions including Fc receptor binding), Applicants submit that even in combination, Gray and Harvill cannot render the claimed invention obvious.

Based on each of the foregoing arguments, Applicants submit that Gray and Harvill cannot be combined to make obvious the invention of claim 1 and those claims depending from claim 1 (*e.g.* 3, 6-8, 10, 29, and 30). Accordingly, Applicants respectfully request that the rejection of the these claims under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Claim 27 is directed to an antibody-based fusion protein comprising a variable domain and a portion of an IgG4 CH2 domain, the C-terminus of which is linked to the N-terminus of a non-Ig protein, wherein said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein. Applicants submit that Gray does not teach an antibody-based fusion protein comprising at least a portion of an IgG4 CH2 domain, the C-terminus of which is linked to the N-terminus of a non-Ig protein to have a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising an IgG1 CH2 domain, the C-terminus of which is linked to the N-terminus of said non-Ig protein. The deficiency of Gray is not remedied by the addition of Harvill. Therefore, even if there were a motivation to combine Gray and Harvill, all limitations of claim 27 are not present in the references. Thus, a *prima facie* case of obviousness has not been made. (See MPEP § 2143.03.)

In the alternative, even if Gray did teach a protein with the requisite *in vivo* half-life, Applicants submit that the deficiencies of Gray would still not be remedied by Harvill. Gray does not teach a variable domain, nor an antibody-based fusion protein comprising a portion of an IgG4 CH2 domain, the C-terminus of which is linked to he N-terminus of a non-Ig protein. Harvill teaches an IgG3-IL2 fusion protein with a variable domain. Recalling that there is no motivation to combine Gray and Harvill because the respective fusion proteins are designed to have mutually antagonistic functions as described *supra*, Applicants further submit that there is no additional motivation to modify Gray to incorporate the variable region of Harvill. Harvill

teaches that variable domains are useful for antigen binding. However, neither Gray nor Harvill provides a motivation for inclusion of an antigen binding domain in the Gray construct. In fact, Gray specifically removed the variable domains to create his CTLA4-IgG4 fusion proteins (see, *e.g.*, col. 34, lines 15-18; col. 29, lines 52-54; and col. 30, lines 18-21), teaching away from the addition of a variable region to the fusion protein of Gray. Applicants therefore submit that even in combination, Gray and Harvill cannot render the invention of claim 27 obvious.

Furthermore, Applicants submit that the deficiencies of Harvill cannot be remedied by the addition of Gray. While Harvill teaches an IgG3-IL2 fusion protein, it does not teach a fusion protein comprising a portion of an IgG4 CH2 domain, the C-terminus of which is linked to the N-terminus of a non-Ig protein. Gray does teach a fusion protein with an IgG4 CH2 domain as required by claim 27. However, Gray teaches away from modifying the fusion protein of Harvill to become IgG4-IL2. As discussed *supra*, Harvill teaches that the IgG3-IL2 fusion protein was designed to maintain the effector functions of human IgG3. (See page 102). Harvill also teaches that the IgG3-IL2 fusion protein was able to maintain its ability to perform effector functions, including complement activation and FcγRI receptor binding. (See Harvill, pgs. 99-100, 103, and Figures 2 & 3). However, Gray teaches that the CH2 region of IgG4 and IgG1 reduce complement activation because they lack the ability to activate complement. (See Gray, col. 4, lines 33-35). Furthermore, Gray teaches that CTLA4-IgG4 "exhibits markedly reduced complement activation and FcR binding activity relative to a wild-type CTLA4-IgG1 construct." (Gray, col. 4, lines 1-4). In assays performed by Gray to test the complement activating ability of CTLA4-IgG4, the protein "did not activate complement... even at a concentration 100-fold higher than that needed for CTLA4-IgG1" (Gray, col. 39, lines 15-17; see also col.39, lines 17-28). Furthermore, Gray states that "the use of IgCγ4 constant region in a CTLA4-Ig fusion protein essentially eliminates the ability of the fusion protein to bind to Fc receptors" (Gray, col. 38, lines 47-50). Therefore, there is no motivation to modify the fusion protein of Harvill to be IgG4-IL2 because the resulting protein would lack the ability to activate complement or to bind to Fc receptors, both desired functions of Harvill's fusion protein. "If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP § 2143.01.

Because modification of the antibody fusion proteins of Harvill to contain an IgG4 CH2 domain would render them unsatisfactory for their intended purpose (activating complement and Fc receptor binding), Applicants submit that even in combination, Gray and Harvill cannot render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection of claim 27 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Gray and Winter

Claim 3 is further rejected over Gray in view of Winter *et al.* (U.S. Patent No. 5,624,821). Applicants submit that if Gray and Winter were combined, all limitations of claim 3 would not be met. Claim 3, dependent on claim 1, is directed to a region of a gene construct encoding an antibody-based fusion protein, the region including at its 5' end nucleotides encoding at least a portion of an IgG1 CH2 domain and at its 3' end, nucleotides encoding a non-Ig protein. However, Gray does not teach an immunoglobulin fusion protein in that orientation, and Winter does not teach or suggest immunoglobulin fusion proteins. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP § 2143.03. A combination of Gray and Winter does not teach or suggest a region of a gene construct encoding an antibody-based fusion protein encoding at its 5' end, a portion of an IgG1 CH2 domain and, at its 3' end, nucleotides encoding a non-Ig protein. Therefore, Applicants submit that claim 3 is not made obvious by Gray in view of Winter. Applicants respectfully request reconsideration and withdrawal of the rejection of claim 3 under 35 U.S.C. § 103(a).

CONCLUSION

Claims 1-3, 4, 6-8, 10, 27, 29, and 30 are pending and presented for reconsideration. Examiner Kapust is invited to telephone the undersigned to discuss any remaining issues.

Respectfully submitted,

Date: July 8, 2004
Reg. No. 48,645

Brian A. Fairchild
Attorney for the Applicants
Testa, Hurwitz, & Thibeault, LLP
High Street Tower
125 High Street
Boston, Massachusetts 02110

Tel. No.: (617) 248-7697
Fax No.: (617) 248-7100

3082156